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건강검진 기관에서 관찰되는 암태아성 항원의 위양성 상승

False-positive Elevations in Carcinoembryonic Antigen Levels at a Health Screening Center

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Background: Although routine screening of carcinoembryonic antigen (CEA) is not recommended for the early diagnosis of colorectal cancers, CEA levels are frequently measured in practice and during opportunistic health screening programs. We evaluated the frequency of false-positive results according to CEA level at a health screening center.
Methods: The medical records of 25,786 participants who underwent a general health check-up and CEA testing at the Seoul National University Hospital Healthcare System Gangnam Center from March 2015 to February 2016 were reviewed. CEA levels were measured using the Architect i2000sr (Abbott Laboratories, USA). The cut-off level for elevated CEA was 5.0 ng/mL.
Results: Among 25,786 participants who underwent CEA screening, 597 (2.3%) had CEA levels >5.0 ng/mL. Among 597 participants with elevated CEA levels, 12 (2.0%) had actual malignancies with CEA levels of 8.3–155.3 ng/mL. Diabetes, smoking, chronic obstructive pulmonary disease, and colonic polyps were considered as causes of false elevation. The false-positive rates of CEA according to level were as follows: 5.1–10.0 ng/mL, 99.5%; 10.1–15.0 ng/mL, 87.2%; 15.1–20.0 ng/mL, 100.0%; >20.0 ng/mL, 33.3%. A subsequent decrease in the CEA level after a 1-month follow-up was observed in 47.6% of all cases with elevated CEA levels.
Conclusions: False elevation in CEA levels in the range of 5.0–20.0 ng/mL is common in patients who underwent testing at a health screening center. False-positive results above 20.0 ng/mL are less common. These data could provide a guide for the interpretation of elevated CEA level at a health screening center.

Key Words: Carcinoembryonic antigen, Mass screening, Biomarkers, Tumor

INTRODUCTION

Despite controversies regarding the expense and ineffectiveness of health screening programs, many countries routinely implement public health screening programs to detect illnesses at an early stage, improve patient outcomes, prevent disease, and promote health [1]. Since the prevalence of cancer and cancer-related mortalities are increasing, cancer screening is one of the most important objectives in health screening programs [2]. Korean opportunistic screening programs include cancer screening and measurement of tumor markers such as prostate-specific antigen, alpha-fetoprotein, carcinoembryonic antigen (CEA), and cancer antigen (CA) 19-9, which are similar to the programs implemented in other East Asian countries [3, 4].

CEA is useful for determining a patient's prognosis, for surveillance following curative resection, and for monitoring response to therapy among patients with colorectal cancer [5]. Most of the guidelines from the American Society of Clinical Oncology, the European Group on Tumor Markers, and the National Academy of Clinical Biochemistry do not recommend tumor marker testing

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for cancer screening due to false elevation associated with various benign conditions. However, the levels of tumor markers are often measured in opportunistic screening programs or evaluated in clinical practice. Thus, there is a definite gap between the stance of the authorities and the routine clinical practice. However, there are no specific clinical guidelines in the screening of elevated CEA levels in apparently healthy people. Elevated CEA levels often lead to unnecessary and extensive workups such as colonoscopy, low-dose chest computed tomography (LDCT), abdominal CT, and mammogram, which are often performed to determine whether colorectal cancer (CRC), lung cancer, or breast cancer is present, respectively.

Our health screening center, the Seoul National University Hospital Healthcare System Gangnam Center, provides comprehensive medical checkups and screening, including endoscopic examinations and imaging studies, and nearly 20,000 people visit our center every year [6].

Although it is well-known that false CEA elevations occur [7], the frequency and range of these false-positive results have not been well described in a modern health screening center with high-quality imaging capabilities. In this study, we collected and analyzed the data from our health screening center to evaluate whether follow-up or further examination following elevated CEA levels is necessary for apparently healthy people.

MATERIALS AND METHODS

1. Study population

The medical records of 25,786 persons who underwent a general health checkup and CEA testing at the Seoul National University Hospital Healthcare System Gangnam Center from March 2015 to February 2016 were reviewed. The study protocol was reviewed and approved by the institutional review board of Seoul National University Hospital (IRB no. H-1606-013-770). Since the current study was performed as a retrospective study using database and medical records, informed consent was waived by the board. The follow-up data were reviewed until December 2017 to monitor for the presence of malignancy.

2. Demographic characteristics, anthropometric data and laboratory findings

Demographic characteristics and anthropometric data were obtained using medical questionnaires, nurse interviews, and health examinations. Data about body mass index (BMI), white blood cell count (WBC), hemoglobin (Hb), platelet count (PLT), glycated hemoglobin (HbA1c), fasting blood sugar (FBS), serum creatinine (Cr), aspartate aminotransferase (AST), alanine aminotransferase (ALT), high-sensitivity C-reactive protein (hs-CRP), and CEA were obtained from the medical records. Blood samples were taken after at least a 12-hour fasting. The serum samples were collected in a tube with a clot activator and serum gel separator. Centrifugation was performed at 3,000 rpm for 10 minutes within 30 minutes of blood draw to prevent glycolysis. WBC, Hb, and PLT were analyzed using an Advia 2120 hematology analyzer (Siemens, Tarrytown, NY, USA). FBS, serum Cr, AST, ALT, and hs-CRP were measured using an ARCHITECT Ci8200 (Abbott Laboratories, Abbott Park, IL, USA). HbA1c was measured using an ADAMS HA 8160 analyzing system (ARKRAY Inc., Kyoto, Japan). CEA was measured with an ARCHITECT i2000sr (Abbott Laboratories) utilizing a chemiluminescent microparticle immunoassay (CMIA). The cut-off level for elevated CEA was defined as 5 ng/mL after validation of reference ranges provided by the manufacturer (0.0–5.0 ng/mL). Serial dilution to exclude spurious elevation caused by interaction with heterophilic antibody was performed when CEA level was over 10.0 ng/mL. One month follow-up of CEA levels was performed in participants with elevated CEA. Decrease in the CEA level was defined as 10% decrease from the initial test or CEA level below 5.0 ng/mL in the follow-up test. There was no standardized protocol workup for elevated CEA, and subsequent investigations or follow-up after 1 month follow-up were often decided by the attending physician. These procedures included colonoscopy, esophagogastroduodenoscopy, abdominal ultrasonography (USG) or CT, LDCT, and mammograms or breast USG.

3. Statistical analysis

All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) 22.0 for Windows (SPSS, Chicago, IL, USA) and MedCalc for Windows version 16.8.4.0 (MedCalc Software, Mariakerke, Belgium). All statistical outcomes were based on two-sided tests and P values <0.05 were significant.

For continuous variables, data were expressed as medians (interquartile ranges) when their distributions were not normal according to the Kolmogorov-Smirnov test ($P<0.001$). Data were expressed as means (SD) when they showed normal distributions.

Pearson's chi-square test was performed to compare the proportional differences in men and women, in participants' smoking habits, and in fecal immunochemical test (FIT) results among CEA subgroups. Independent-sample *t*-test was performed to compare age, BMI, and levels of WBC, PLT, HbA1c, FBS, serum creatinine, AST, ALT, hs-CRP, and CEA among HbA1c subgroups.

RESULTS

The demographic characteristics of all participants and subgroups according to CEA level are shown in Table 1. The median and interquartile ranges of the CEA level of all participants was 1.6 (1.1–2.3). Among the 25,786 participants who underwent CEA testing, 597 (2.3%) had CEA levels >5.0 ng/mL. Subgroups were divided according to CEA level: CEA ≤5.0 (N=25,189) and CEA >5.0 (N=597). Mean age and levels of WBC, Hb, HbA1c, FBS, serum Cr, AST, and hs-CRP were significantly higher in the elevated CEA group. The percentages of male participants, smokers, participants with diabetes, participants with chronic obstructive pulmonary disease (COPD) or inflammatory lesion in the lungs, participants with colonic polyp, and participants with positive FIT were also higher in the elevated CEA group.

Among the 597 participants with elevated CEA levels, 12 (2.0%) had actual malignancies, including colorectal (N=5), lung (N=4), breast (N=1), and pancreatobiliary cancer (N=2) (Table 2). Colonic polyp, diabetes, smoking, COPD, and inflammatory lesions of the lung were the benign conditions associated with elevations in CEA levels. However, 38.2% of participants had elevated CEA levels but no specific clinical condition related to CEA elevation, and 53.5% of these participants had normal CEA levels at the 1-month follow-up test.

To investigate the clinical utility of CEA in cancer screening, case reviews were performed among patients with elevated CEA levels and malignancy (Table 3). Four participants were known

Table 1. Characteristics of the study population

Parameter	All (N=25,786)	CEA ≤5.0 (N=25,189)	CEA >5.0 (N=597)	*P* value*
Age, yr (mean ± SD)	56.7 ± 8.7	51.0 ± 11.4	57.4 ± 10.7	0.189
Sex, N (%)				
Male	13,945 (54.1)	13,469 (53.5)	476 (79.7)	<0.001
Female	11,841 (45.9)	11,720 (46.5)	121 (20.3)	
Smoking, N (%)				
Current smoker	1,480 (5.7)	1,434 (5.7)	46 (7.7)	0.023
Non-smoker	24,306 (94.3)	23,755 (94.3)	551 (92.3)	
Diabetes, N (%)	1,740 (6.7)	1,646 (6.5)	94 (15.8)	<0.001
COPD or inflammatory lesion in lung, N (%)	1,440 (5.6)	1,400 (5.4)	40 (6.6)	<0.001
Colonic polyp, N (%)	4,420 (17.1)	4,163 (16.5)	257 (43.0)	<0.001
BMI (kg/m^2)	23.1 (21.0–25.2)	23.1 (21.0-25.2)	23.9 (21.9-25.7)	0.768
WBC (×10^3/μL)	5.4 ± 1.5	5.4 ± 1.5	6.3 ± 1.9	<0.001
Hb, g/dL	14.4 ± 1.5	14.4 ± 1.5	15.0 ± 1.4	0.041
Platelet (×10^3/μL)	228 ± 52	228 ± 52	221 ± 52	0.536
HbA1c, %	5.7 ± 0.6	5.7 ± 0.6	6.0 ± 1.0	<0.001
FBS, mg/dL	100 ± 18	100 ± 18	110 ± 32	<0.001
Serum creatinine (mg/dL)	0.82 ± 0.19	0.82 ± 0.19	0.87 ± 0.17	0.043
AST (IU/L)	24 ± 12	24 ± 12	27 ± 15	<0.001
ALT (IU/L)	24 ± 18	24 ± 18	26 ± 18	0.909
hs-CRP (mg/dL)	0.12 ± 0.37	0.11 ± 0.36	0.18 ± 0.70	<0.001
FIT, N (%)†				
Positive	164 (0.9)	155 (0.9)	9 (2.1)	0.019
Negative	17,239 (99.1)	16,826 (99.1)	413 (97.9)	
CEA, ng/mL	1.6 (1.1–2.3)	1.6 (1.1–2.2)	6.1 (5.4–7.3)	<0.001

Values were presented as mean (SD), median (interquartile range), or number (percentage).
*CEA ≤5.0 vs. CEA >5.0 ng/mL; †Data were missing in 8,383 participants.
Abbreviations: CEA, carcinoembryonic antigen; COPD, chronic obstructive pulmonary disease; BMI, body mass index; Hb, hemoglobin; HbA1c, glycated hemoglobin; FBS, fasting blood sugar; AST, aspartate aminotransferase; ALT, alanine aminotransferase; FIT, fecal immunochemical test; CEA, carcinoembryonic antigen; CA 19-9, cancer antigen 19-9.

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cancer patients on monitoring, and seven were newly diagnosed with colorectal, lung, or breast cancer at checkup. The range of CEA levels in these patients newly diagnosed with malignancies was 8.3–155.3 ng/mL. The diagnoses of the four newly diagnosed colorectal cancer patients had their diagnoses confirmed by an additional colonoscopic examination after the initial test showed elevated CEA levels. Among the four participants with elevated CEA levels who were newly diagnosed with colorectal cancer, three had FIT-positive results and one had FIT-negative results.

Among 585 participants who had elevated CEA levels and no evidence of malignancy, 544 (93.0%) had a CEA level of 5.1–10.0 ng/mL, 34 (5.7%) had 10.1–15.0 ng/mL, 5 (0.9%) had 15.1–20.0 ng/mL, 1 (0.2%) had 20.1–25.0 ng/mL, and 1 (0.2%) had 25.1–30.0 ng/mL (Table 4). In 544 participants with CEA levels of 5.1–10.0 ng/mL with no malignancy, 275 (50.6%) had a subsequent decrease in the CEA level at 1-month follow-up. Among 34 participants with CEA levels of 10.1–15.0 ng/mL with no malignancy, 8 (20.5%) had a subsequent decrease in the CEA level at 1-month follow-up. A follow-up test was performed in two participants after smoking cessation, in one participant after removal of colorectal adenomatous polyps, and two participants after discontinuing herbal medicine. Five (20.0%) participants with CEA levels between 15.1 and 20.0 ng/mL and no malignancy were identified as current smokers. Only 1 (20.0%) participant were able to quit smoking and showed a decrease in CEA levels (9.9 ng/mL) at 1-month follow-up. Two participants with a CEA level ≥20.1 ng/mL and without malignancy did not show a decrease in the CEA level at follow-up. Of

Table 2. Diagnosis of patients with elevated carcinoembryonic antigen levels

Diagnosis	No. of participants (%)	CEA (ng/mL)
Colorectal cancer	5 (0.8)	11.8 (9.8–17.0)
Lung cancer	4 (0.7)	16.9 (11.1–24.2)
Breast cancer	1 (0.2)	N/A
Pancreatobiliary cancer	2 (0.3)	N/A
Colonic polyp	223 (37.4)	6.0 (5.3–6.9)
Diabetes	38 (6.4)	6.3 (5.4–7.6)
Diabetes and colonic polyp	10 (1.7)	7.5 (5.8–11.5)
Diabetes and smoking	22 (3.7)	6.6 (5.7–8.5)
Diabetes, smoking, and colonic polyp	24 (4.0)	6.0 (5.3–6.7)
COPD or inflammatory lesion in the lung	40 (6.6)	5.7 (5.5–7.0)
No specific clinical condition	228* (38.2)	5.9 (5.3–7.4)
Total	597 (100.0)	6.1 (5.4–7.3)

*The carcinoembryonic antigen level of 122 out of 228 participants (53.5%) normalized in a follow-up test.
CEA levels were presented as median (interquartile ranges).
Abbreviations: CEA, carcinoembryonic antigen; COPD, chronic obstructive pulmonary disease; N/A, not applicable.

Table 4. False-positive rates of CEA according to level (N=597)

CEA level (ng/mL)	Participants with proven malignancy, N	Participants without evidence of malignancy, N*	Subsequent decrease in the CEA level after follow-up, N† (%)	False-positive rates (%)
5.1–10.0 (N=547)	3	544	275 (50.3)	99.5
10.1–15.0 (N=39)	5	34	8 (20.5)	87.2
15.1–20.0 (N=5)	0	5	1 (20.0)‡	100.0
20.1–25.0 (N=3)	2	1§	0 (0.0)	33.3
>25.0 (N=3)	2	1‖	0 (0.0)	33.3

*No evidence of cancer on low-dose chest computed tomography (CT), abdomen CT, thyroid ultrasonography, colonoscopy, and esophagogastroduodenoscopy; †The percentage of decrease in the CEA level after follow-up according to each CEA level group; ‡The initial and follow-up levels of CEA were 19.6 and 9.9 ng/mL, respectively; §The participant's CEA level was 20.8 ng/mL; ‖The participant's CEA level was 30.4 ng/mL.
Abbreviation: CEA, carcinoembryonic antigen.

Table 3. Case reviews for elevated carcinoembryonic antigen levels with malignancy

No.	Sex	Age	CEA (ng/mL)	Diagnosis	FIT	History of smoking
38062	M	54	21.8	Colorectal cancer, newly diagnosed	Positive	Ex-smoker
21494	M	86	9.9	Colorectal cancer, newly diagnosed	Positive	Non-smoker
8052	F	73	11.8	Colorectal cancer, newly diagnosed	Positive	Non-smoker
31435	M	65	12.1	Colorectal cancer, newly diagnosed	Negative	Ex-smoker
41541	M	77	25.5	Lung cancer, newly diagnosed	N/A	Current smoker
48991	M	65	10.3	Lung cancer, newly diagnosed	N/A	Non-smoker
13491	F	61	8.3	Breast cancer, newly diagnosed	N/A	Non-smoker
18613	M	77	155.3	Cholangiocarcinoma, newly diagnosed	N/A	Ex-smoker
10798	F	76	9.6	Colorectal cancer, on monitoring	N/A	Non-smoker
40687	M	45	13.5	Lung cancer, disease progression	N/A	Ex-smoker
27469	F	71	20.3	Lung cancer, disease progression	N/A	Non-smoker
35923	M	61	12.7	Pancreatic cancer, disease progression	N/A	Non-smoker

Abbreviations: CEA, carcinoembryonic antigen; FIT, fecal immunochemical test; N/A, not applicable.

these two participants, one had patchy ground-glass opacities on LDCT, suggesting inflammation, while no specific conditions were detected in the other patient on esophagogastroduodenoscopy, colonoscopy, LDCT, abdominal CT, or thyroid USG that may explain the elevated CEA levels.

Further follow-up CEA test were performed in participants who did not show a decrease in CEA levels at 1-month follow-up. The proportions of participants who showed a decrease in CEA levels in further follow-up were analyzed according to their clinical conditions: colonic polyp, 19/35 (54.3%); smoking, 22/41 (53.7%); COPD or inflammatory lesion in lung 30/58 (51.7%); diabetes, 12/28 (42.9%); diabetes and colonic polyp, 3/10 (33.3%); diabetes and smoking; 15/25 (60.0%); and diabetes, smoking, and colonic polyp, 14/24 (58.3%).

The false-positive rates of CEA according to their levels were as follows: 5.1–10.0 ng/mL, 99.5%; 10.1–15.0 ng/mL, 87.2%; 15.1–20.0 ng/mL, 100.0%; 20.1–25.0 ng/mL, 33.3%; and >25.0 ng/mL, 33.3%. Using a CEA cut-off value of 20.0 ng/mL, the negative predictive value and positive predictive value for detecting malignancy were 100.0% and 66.7%, respectively.

DISCUSSION

We investigated the causative clinical conditions for elevated CEA in a health screening center. Although the limited value of CEA in cancer screening is well understood, 4 of the 25,786 participants were diagnosed with colorectal cancer after detection of elevated CEA level. Of the four newly diagnosed colorectal cancer patients, only one showed negative FIT results, which indicated low sensitivity for advanced colorectal cancer [8].

Although false-positive CEA levels frequently occur, their frequency and range have not been previously well characterized in a health screening context. Indeed, CEA for cancer screening is included in nearly all Korean opportunistic health checkups; however, there is no specific clinical guideline recommending the performance of follow-up test or further work-up for elevated CEA in apparently healthy people. One report by Litvak et al. described false-positive elevations in 728 patients who underwent resection of locoregional colorectal cancer and who had an increase in CEA level during follow-up [7]. This could not be directly applied since the subject population was different from that of a health screening setting. The present study provides the first large, modern data set for determining the frequency and range of false-positive CEA measurements in a health screening setting.

In our study, false-positive rates of CEA in the screening of cancer were much higher when CEA levels were ≤20.0 ng/mL. Most of the false-positive elevations in CEA levels were below 10.0 ng/mL. Approximately 50.6% of falsely elevated CEA at the ≤10.0 ng/mL level showed a subsequent decrease in CEA levels on follow-up test. Persistent CEA levels over 31.0 ng/mL were all true positive.

Several clinical conditions have been reported to be related to CEA elevation, including COPD [9], pneumonia [10], and colonic polyps [11], as observed in our study. In our study, diabetes was present in 15.7% of participants with elevated CEA levels. Furthermore, the FBS and HbA1c levels were higher in the elevated CEA group than in the normal CEA group. Similarly, a previous study showed that subjects with type 2 diabetes mellitus had a higher CEA level than healthy controls [12]. Furthermore, HbA1c positively correlated with CEA in patients with diabetes [13]. The pathophysiologic explanation for the association between elevated CEA levels and glycemic control is unknown. It has been hypothesized to be an increased cancer risk in patients with diabetes either due to tumor cell proliferation or to inflammatory changes associated with diabetes [12].

False elevation of CEA caused by smoking in our study population showed levels up to 19.6 ng/mL. A previous study showed increases in CEA mRNA expression and protein expression in the lung tissue of smokers compared with those in non-smokers and ex-smokers [14], and this result supports our finding of elevated CEA levels in smokers. In addition, smoking cessation was shown to decrease serum CEA levels [15], which was also observed in our study.

The mechanism for increase in CEA levels in participants with colonic polyp has not been elucidated yet. However, previous study by Tong et al. [16] reported that the recurrence of colorectal polyp was related to serum CEA levels. Since colorectal cancer primarily arises from the polyps of the colon and CEA is a product of columnar and goblet cells in the normal colon and colonic cancer, the serum levels of CEA might increase 4.5 to 8 months before the development of cancer symptoms.

The false-positive rate of CEA for detecting cancer was only 33.3% when the CEA levels were above 20 ng/mL by the ARCHITECT i2000sr. There was no false-positive elevation of CEA levels

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over 30.4 ng/mL. In particular, 47.6% of patients with elevated CEA levels showed a decrease in CEA levels at 1-month follow-up. This phenomenon was much more prevalent for CEA levels of 5.1–10.0 ng/mL (50.3%). Therefore, follow-up testing instead of initial extensive workup for elevated CEA could be an alternative method of excluding malignancy. Particularly in smokers, follow-up testing after smoking cessation would prevent further unnecessary CT or endoscopic examinations.

Although only 2.0% of participants with elevated CEA had malignancy, 4 (33.3%) colorectal cancer patients were newly diagnosed on further workup. Among these patients, one colorectal cancer patient showed a negative FIT result; therefore, additional colonoscopy was performed solely due to elevated CEA levels and detected colorectal cancer.

A limitation of this study was that the measurement method for CEA is not yet standardized [17]; therefore, the cut-off value described in this study cannot be universally utilized. It could only be utilized in a center using the ARCHITECT i2000sr. Furthermore, there was no standardized work up protocol for elevated CEA. Therefore, further follow-up or investigations were often decided by the attending physician.

Our data suggested that slight elevation in the CEA level (≤20.0 ng/mL) has a substantial likelihood of representing a false-positive elevation using i2000sr as a measurement method in an apparently healthy person in a health screening center. However, serum CEA levels greater than 20.0 ng/mL are predictive of malignancy; therefore, diagnostic procedures should be performed immediately. These data could provide a guide for the interpretation of elevated CEA levels detected at a health screening center.

요 약

배경: 대장암의 조기진단을 위해 암태아성 항원(carcinoembryonic antigen, CEA)을 선별검사로 사용하는 것은 추천되지 않으나, 실제 진료실 및 일반 건강검진 프로그램에서 CEA 수치를 빈번히 측정하고 있다. 본 연구에서는 건강검진 기관에서 관찰되는 CEA 위양성 빈도를 CEA 수치에 따라 분석하였다.

방법: 2015년 3월부터 2016년 2월까지 서울대학교병원 강남센터에서 건강검진을 받은 25,786명을 대상으로 의무기록을 분석하였다. CEA는 ARCHITECT i2000sr (Abbott Laboratories, USA)로 측정하였다. CEA 상승 기준은 5.0 ng/mL를 초과하는 경우로 정하였다.

결과: 25,786명 중 597명(2.3%)이 CEA 수치가 5.0 ng/mL를 초과하였다. 이 중, 12명(2.0%)은 악성종양이 있었으며 CEA 수치 분포는 8.3-155.3 ng/mL이었다. 당뇨병, 흡연, 만성폐쇄성폐질환, 대장 용종이 거짓 상승의 요인으로 추정되었다. CEA 수치에 따른 위양성률은 다음과 같다: 5.1–10.0 ng/mL, 99.5%; 10.1–15.0 ng/mL, 87.2%; 15.1–20.0 ng/mL, 100.0%; >20.0 ng/mL, 33.3%. CEA가 상승한 사람들 중 47.6%는 1개월 후 추적 시 그 수치가 감소하였다.

결론: 건강검진 수진자에서 CEA 수치는 5.0–20.0 ng/mL까지 거짓 상승되는 경우가 흔하며, 20.0 ng/mL를 초과하는 위양성은 덜 흔하게 관찰된다. 본 연구의 결과는 건강검진 수진자에서 CEA 수치가 상승된 경우의 해석에 참고할 수 있겠다.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

No potential conflicts of interest relevant to this article were reported.

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